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EXAMINER
KUSHAN, J

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DATE MAILED: 04/23/91

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THIS IS A COMMUNICATION FROM THE EXAMINER IN CHARGE OF YOUR APPLICATION
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/28/91 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 21-24 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-20 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 21-24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The claims pending in this action are new claims 21 to 24. These claims are drawn to (a) factor IX protein having a recited purity level, activity, and other particular features, and (b) a method for treating factor IX deficiency. All other claims have been canceled.

17. Claims 21 to 24 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to monomorphic essentially full sequence factor IX proteins. See MPEP 706.03(n) and 706.03(z).

The presented claims are drawn to monomorphic (e.g. expressed from a single cDNA) species of factor IX, where the factor IX protein retains enough of the overall sequence to yield a stated minimum percentage of the activity of the native protein. This feature has for the first time been explicitly recited in the claim language, and when considered with the additional modification of the claim to recite the origin of the sequence, has defined a class of compounds which is not directly supportable from the original disclosure.

The original disclosure of applicant does not identify which minimum portions of the native factor IX protein can be used to yield and retain the recited 90% activity level. Nor has this disclosure provided any guidance as to which residues in the native sequence may be altered or deleted with concominant retention of the 90% activity level. As the disclosure fails to provide direction to the person of

ordinary skill as to how to produce the range of species explicity claimed, the presented claims lack support from said disclosure.

Applicant's attention is directed to the recent decision of the Federal Circuit in Amgen v. Genetics Institute, 18 U.S.P.Q.2d 1016,1028, where the court held

> It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.

The court upheld the finding of invalidity of a claim which, like applicant's claim, defined a range of species purely in the functional result desired under a lack of enablement (e.g. 35 U.S.C. 112, first paragraph). The failure to provide direction and guidance as to how to produce the additional species falling with the broad scope of the claim renders the claimed breadth unsupportable. Shifting to the person of ordinary skill the burden of ascertaining which substitions, deletions, and additions could possibly yield analogs having the stated activity equates to undue amounts of experimentation.

To overcome this point of the rejection, applicant should restrict the scope of the claims to full native sequence Factor IX expressed from a single cDNA construct.

18. Claims 1,10-12, and 14 to 25 are rejected under 35 U.S.C. 103 as being unpatentable over Suomela et al., or Osterud et al., in view of Schwinn.

The arguments of applicant, and the amendments to the claims have been fully considered but are not persuasive. Accordingly, this rejection is maintained.

The claims now recite that the factor IX protein is the product of expression of a single cDNA (e.g. single allellic form), along with qualifications on the overall size or structure of the factor IX protein, minimum activity of the protein, and a recitation that the protein is free from all human plasma constituents and poxviruses.

The examiner agrees with applicant's point regarding the requirement that the claimed protein be defined as having absolute purity. This point is withdrawn.

As was summarized in the last office action, the claimed factor IX product and its method of use would have been considered to have been prima facie obvious to the person of ordinary skill in this art. Applicant has advanced two theories as to why the prior art does not render obvious the claimed compositions.

First, applicant argues that since the claims are limited to a monomorphic form of factor IX, and that the prior art only suggests (generally) mixtures of two allellic forms, that the prior art is incapable of suggesting the instantly claimed protein. The declaration of Dr. Brownlee was fully considered in the last office action, and the

weight of this distinction was accorded to the benefit of applicant. Specifically, the evidence of allelic mixtures of the protein was acknowledged by the examiner to justify withdrawal of the rejections based upon anticipation. The significance of this allelic variation, however, standing alone cannot justify a conclusion that the prior art factor IX would not have made obvious the claimed protein, when said prior art is taken in view of Schwinn. No detectable significance has yet to be shown to be attributable to the administration of allelic, as opposed to monomorphic compositions of factor IX. Arguing that a minor fact discovered subsequent to the filing of the present application can justify a conclusion that the expressed protein should not be considered to have been prima facie obvious is not convincing. Such a showing has significance only to establish an absence of anticipation.

The next point argued by applicant is that the purification process of the secondary disclosure, namely that of Schwinn et al., is incapable of yielding a composition which is free from all human plasma constituents. This argument focuses upon a presumption that the prior art starting material (e.g. factor IX isolated from pooled human plasma), when purified by the Schwinn process, will remain dangerous due to the presence of undetectable levels of contamination by HIV and hepatitus viruses. This presumption, however, is not been supported by convincing

evidence. Applicant's earlier declaration makes it clear that certain plasma constituents apparently remain after the purification procedures defined by the primary disclosures have been practiced. The examiner is not contesting this point. The point which is the examiner disagrees with is the significance of this contamination. Unless applicant is prepared to show that the factor IX compositions further purified by the Schwinn process contain contamination which precludes their use in methods for treating factor IX deficiencies, an argument that the prior art teachings taken together do not render the claimed compositions prima facie obvious simply because of the presence of said plasma constituents will not be considered persuasive. The person of ordinary skill in this art would have recognized that the safety of the compositions was a necessary prerequisite to their use in humans, and would have practiced the process of Schwinn et al., until reasonably assured of the safety of the factor IX composition.

The prima facie determination of obviousness set forth in the last office action has not been rebutted by applicant. Accordingly, this rejection is maintained for the reasons of record. Applicant may wish to consider submission of evidence of secondary considerations to overcome this presumption of prima facie obviousness, if possible.

19. No claims are allowed.

20. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

21. Applicant may wish to adjust the format of the pending claims with respect to the recitation of activity levels. Specifically, applicant is encouraged to replace "ratio:" with the phrase "ratio <u>of the</u>" and replace the line drawn in the claim with the phrase "<u>divided by the</u>". Such an amendment will ensure clarity and avoid problems in interpretation of the claim.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kushan whose telephone number is (703) 308-0196. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

jpk
April 19, 1991

Esther Kepplinger

ESTHER L. KEPPLINGER
SUPERVISORY PATENT EXAMINER
GROUP ART UNIT 182